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14. ABSTRACT This study examines the efficacy of two cognitive-behavioral treatments for PTSD-related recurrent nightmares and other sleep difficulties in Veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) in a randomized controlled trial. Participants will be 115 OEF/OIF Veterans in outpatient treatment for PTSD at one of two study sites, the Philadelphia VAMC or the VACHS, West Haven, CT. During Year Four of this award, data collection was ongoing at the Philadelphia sites (PVAMC and PVAMC affiliated outpatient clinics). Data will be analyzed at the end of the data collection period, and therefore research findings are not yet available. Sixty-five patients have been enrolled in the protocol to date.					
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Section I: Introduction

A substantial proportion of Veterans returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) have significant psychological symptoms related to traumatic war zone exposure, including recurrent nightmares and other sleep disturbances. Nightmares are generally distressing and difficult to treat, often persisting despite successful resolution of other Posttraumatic Stress Disorder (PTSD) symptoms. A cognitive-behavioral treatment (CBT), Imagery Rehearsal (IR), appears to have promise for successfully treating nightmares. This study investigates the efficacy of IR in treating OEF/OIF veterans, many of whom likely have mild to moderate traumatic brain injury (TBI). There are three main objectives of this study: 1) to examine the efficacy of IR, combined with psychoeducation about PTSD and nightmares and standard CBT for insomnia (IR + PPCI), compared to psychoeducation about PTSD and nightmares and CBT for insomnia (PPCI) alone, in reducing nightmare frequency and improving global sleep quality in OEF/OIF veterans with PTSD; 2) to determine whether there are moderating effects of neurocognitive impairment on the efficacy of these two forms of CBT for nightmares; and 3) to explore possible neurobiological correlates of treatment-related changes in nightmare frequency and sleep quality, focusing on noradrenergic systems. One hundred and fifteen OEF/OIF Veterans enrolled in treatment for PTSD at the Philadelphia VA Medical Center (PVAMC) or the VA Connecticut Health Care System (VACHS), West Haven, CT, will be randomized to one of two individual treatments: IR + PPCI or PPCI alone. Participants are referred by their mental health treatment providers and assessed for PTSD and war zone-related nightmares. Participants complete a battery of computerized neuropsychological tests at baseline and are stratified in their randomization to either group depending on the results. Once randomized, participants meet for 6 weekly individual sessions of IR + PPCI or PPCI alone. Participants complete self-report questionnaires assessing nightmares, sleep quality, PTSD, and depression, at baseline, immediately after treatment, and again three and six months after treatment. Additionally, participants provide saliva samples for measurement of salivary alpha-amylase, a marker of peripheral noradrenergic activity, both before sleep onset and upon awakening, for two nights before treatment and for two nights before the first post-treatment assessment.

Section II: Progress to Date on 5 Study Tasks in Approved Statement of Work:

1. Obtaining approvals for the study protocol at the study locations.

A. Philadelphia VAMC/University of Pennsylvania:

- Regulatory review of the initial protocol was completed by the PVAMC IRB on 3/13/2008 and the DoD HRPO on 2/13/2009. During the current reporting year, we have submitted the following amendments to this protocol: Room change, addition of medical student to staff form, removal of Danielle Claus, addition of new assessment measure 'Lucid Dreaming Scale' (10/3/12); Addition of Coatesville VAMC as a recruitment site (3/13/2013).

B. VACHS, West Haven/Yale University:

- Regulatory review of the initial protocol was completed by the VACHS IRB and Research and Development Committee on 6/5/2008 and by the Yale University IRB on 11/12/2008. The DoD HRPO approved this protocol on 2/24/2009. The protocol for this study site was closed at VACHS (3/7/12) and Yale University (10/13/11).

PROBLEMS ENCOUNTERED:

- Delay in transfer of data to primary site: There was a delay in obtaining access to the computerized record system at VACHS to allow verification of inclusion and exclusion criteria for those participants enrolled there. We are in the process of checking the computerized records.

2. *Recruitment, assessment and randomization of 109 participants at the PVAMC site and 6 at the VACHS site (total N=115).*

A. PVAMC:

- During this reporting period, the PIs had several phone conferences with DoD staff to determine the best course of action for the remainder of this project. We currently are continuing to recruit participants across all Philadelphia sites, and the recruitment rate remains at 2-3 enrolled participants per month.
- The PVAMC site was the source of 31 referrals from treatment providers during the reporting period. Eighty-four percent (26) were male, and 16% (5) were female. Forty-eight percent (15) were African-American, 7% (2) Hispanic, 42% (13) Caucasian, and 3% (1) was of unknown ethnicity. Assessments were scheduled with 15 potential participants. 13 veterans were enrolled in the study at the PVAMC site. Six were randomized to IR + PPCI and seven to PPCI alone.
- The Philadelphia VAMC-affiliated CBOCs were the source of 62 referrals from treatment providers during the reporting period. Eighty-nine percent (55) were male, and 11% (7) were female. Approximately twenty-seven percent (17) were African-American, 5% (3) Hispanic, 53% (33) Caucasian, and 15% (9) of other ethnicity. Assessments were scheduled with 19 potential participants: 13 completed both assessment sessions (one participant is on hold due to long recovery from knee surgery). Twelve participants were enrolled in the treatment study in the past year: Five were randomized to IR + PPCI and seven to PPCI alone. In addition, two more participants signed a consent to be treated, but have not yet randomized due to their work schedules and medical issues.

PROBLEMS ENCOUNTERED:

- Technical issues: The PVAMC updated all computers to Windows 7 during this reporting period. This led to some disruption in our ability to conduct the computerized neuropsychological assessment at some of the CBOCs. Therefore, while we continued to enroll participants, we missed collecting some neuropsychological data.

- Loss of two study therapists: The therapist at the Camden CBOC left her position after her maternity leave. Currently, one of the PIs, Dr. Harb, is treating any participant referred through the Camden CBOC. In addition, the therapist at the Willow Grove CBOC needed to leave the study as of June 2013. We will continue to accept referrals from this CBOC; however, Veterans will need to be willing to travel to another CBOC or to the PVAMC to receive the 6-week treatment.
- Recruitment challenges: We are confident that we are aware of all OEF/OIF Veterans scheduled for appointments in the Philadelphia VA system who may be eligible for the study. With a HIPAA waiver and through careful review of all upcoming appointments of mental health and post-deployment primary care providers at the PVAMC and the CBOCs, we are able to identify potential participants. We regularly alert a provider, before the appointment, to the 'potential candidate' status of an OEF/OIF Veteran she/he is scheduled to see. Due to the high no-show rate and other exclusionary factors, such as patient preference and/or comorbid problems (e.g., problem drinking or exclusionary diagnoses), only a fraction of these identified Veterans become referrals to our study. Similar to the experience of other clinicians and investigators, we find that this group of Veterans is ambivalent about seeking treatment. They have a multitude of life responsibilities, and they often have post-deployment symptoms that can interfere with consistent attendance at assessment and/or treatment sessions. We are confident that we are doing everything possible to engage interested Veterans in this intervention study, and we have had considerable success with our recruitment strategy. We have increased our recruitment rate, and we are confident that we will be able to continue our current recruitment rate even through the difficult recruitment months of the summer season.
- New recruitment site: After the January phone conference with DoD personnel including Ms. Inna Williams, we pursued and set up a new recruitment site for this study. The Coatesville VAMC (CVAMC) is approximately 1 hour from the Philadelphia VAMC, and its CBOCs are between 30 and 50 minutes from the PVAMC. We completed the regulatory process (through the CVAMC and PVAMC IRBs and the DoD HRPO) in April 2013. However, we have not yet activated the site. We are not hiring new staff for the CVAMC site, and we have been reluctant to shift staff effort from Philadelphia and its CBOCs. We investigated limiting our initial recruitment to the one CVAMC CBOC closest to Philadelphia, but have not yet been offered the necessary office space. Also, we are uncertain about the projected recruitment rate through CVAMC and its CBOCs. We continue to assess this situation, with the help of CVAMC providers and research staff who have been very enthusiastic about collaborating with us. We currently are trying to put in place a procedure for accepting referrals from CVAMC who are able to be assessed and treated at the PVAMC or a PVAMC CBOC, where space is available.

Table 1: Recruitment at PVAMC and affiliated CBOCs for reporting period

Recruitment Site	Referred	Assessed*	Enrolled PPCI+IR	Enrolled PPCI
Willow Grove CBOC	9	0	1	0
Camden CBOC	4	1	1	1
Gloucester CBOC	21	7	3	1
Ft. Dix CBOC	28	5	2	3
PVAMC	31	13	6	7
Total	93	26	13	12

*Note: Some Veterans were assessed in the previous reporting year and enrolled during this reporting period.

B. VACHS, West Haven:

- The VACHS site received 22 referrals from treatment providers and 14 self-referrals, of which 89% were male and 11% were female, with an average age of 35. Fifty-eight and three tenths percent were Caucasian, 22.2% African-American, and 19.4% Hispanic/Latino. Assessments were scheduled with 12 potential participants, and six Veterans completed the second assessment. Six participants were enrolled in the treatment study.
- The VACHS site has been closed to enrollment since 4/2010.

3. Administration of six sessions of the protocol treatments to participants.

A. Philadelphia VAMC/CBOCs:

- Of the 25 Veterans enrolled at the PVAMC and its affiliated CBOCs this year, 12 have completed all six treatment sessions and are in the follow-up phase of the study. Three are currently in treatment, five received some treatment before withdrawing from the study, and four have been randomized and not yet treated. Of those enrolled this year, one has already completed all follow-up visits.
- Treatment fidelity: During Year One of this award, a detailed supervision plan as well as fidelity rating procedures were developed. Study supervisors, Drs. Philip Gehrman and Andrea Phelps, review treatment tapes, and weekly supervision calls with study supervisors are attended by all therapists; these sessions have ensured treatment protocol adherence across sites.
- Training of additional therapist: After losing two study therapists during this reporting period, we have identified another PVAMC psychologist, Dr. Beth Rhoads, interested in participating in this study as a study therapist. She is currently working to complete all regulatory requirements, and she is being trained as a therapist by Dr. Harb. We anticipate that she will be ready to be assigned her first case in July 2013.

B. VACHS, West Haven:

- Of the six participants enrolled in the treatment study over the course of VACHS's participation, one Veteran withdrew after completing one session of treatment. Five Veterans completed the treatment and all follow-up assessments.

4. *Follow-up: re-assessment for detection of treatment effects immediately post-treatment and maintenance of benefits at 3 months and 6 months post-treatment.*

A. Philadelphia VAMC/CBOCs:

- Fourteen Veterans are currently active in the follow-up phase of the study, and one Veteran completed all study follow-ups this year. Of the fourteen in follow-up, all have completed the first post-treatment assessment, and nine have completed the 3-month follow-up. We have lost no Veterans to follow-up this year.
- In total to date, 43 Veterans have completed the final 6-month follow-up assessment for the study. We had five drop-outs during the follow-up period: four Veterans completed treatment and the first post-treatment assessment but did not return to complete the 3- or 6-month follow-up; one participant completed only the 3-month follow-up. Finally, fifteen Veterans dropped out of the study during treatment and nine after randomization but before receiving any treatment.

B. VACHS, West Haven:

- Five participants completed all post-treatment and follow-up assessments as of December 2010.
- No Veterans remain actively enrolled in this study at VACHS.

5. *Statistical analysis of the data and manuscript preparation.*

- The project is in the data collection phase, and no statistical analyses are currently being completed. Limited data are analyzed for the purpose of poster presentations (see below).

Philadelphia VAMC:

- Entry of data from assessed and enrolled participants has been ongoing at the PVAMC. For budgetary reasons, we had to reduce the effort of our study assessor and of our research coordinator. Therefore, concurrent data entry and checking will no longer be possible while study recruitment is ongoing.
- Data from the closed VACHS site is still in the process of being verified, and no data have been entered into study databases.

Section III: Key Research Accomplishments:

- Completion of lengthy regulatory reviews at PVAMC, Yale University, VACHS, and the DoD HRPO.
- Hiring and training of staff, most recently new staff to provide treatment at the

PVAMC.

- Participant recruitment is ongoing at the PVAMC site and its affiliated CBOCs.
- Extensive efforts to boost the recruitment rate. These have included modification of the protocol to allow active duty personnel seen at the VA to be included in this study.
- Successful shift of recruitment from the VACHS site, which discontinued recruitment of participants for the study in April 2010, to the PVAMC-affiliated CBOCs.
- Successful increase in recruitment rate over the years of the awards, and steady recruitment over the last 3 years, see Figures 1 and 2, below.

Figure 1. Total number of Veterans enrolled since start of enrollment at all sites

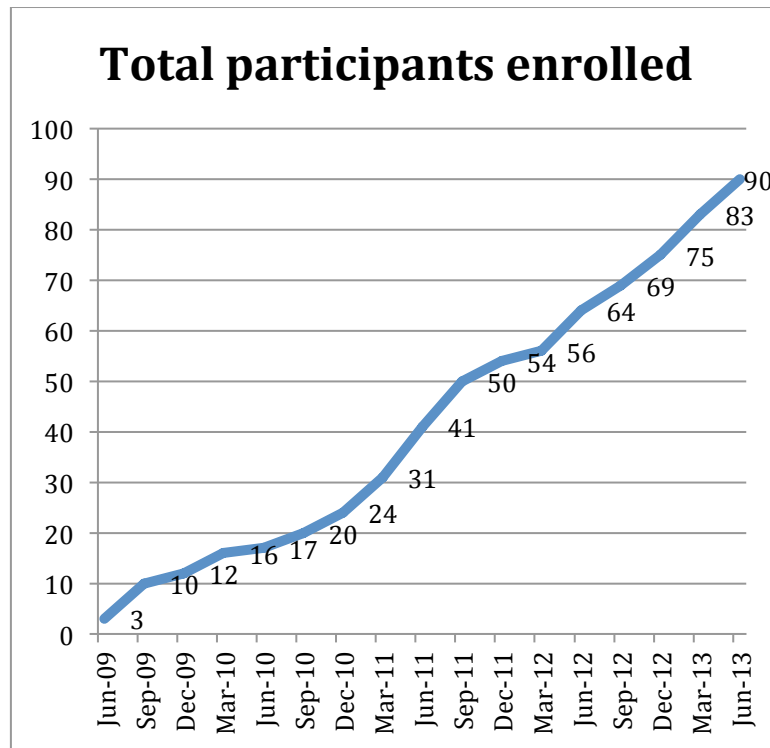
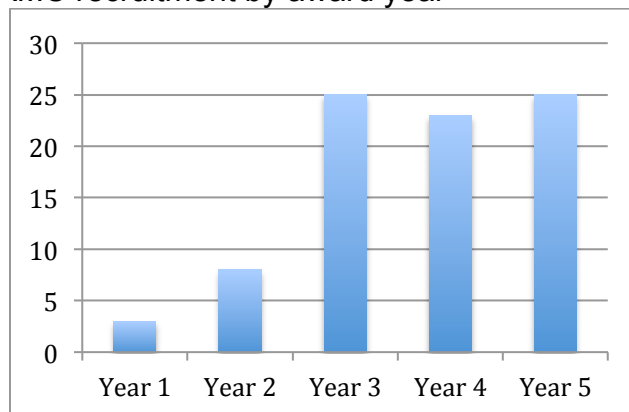


Figure 2. PVAMC recruitment by award year



Section IV: Reportable Outcomes: Presentations:

Poster presentation:

Harb, G. C., Cary, M., Gehrman, P., Ross, R. (2013). *The Symptoms of OEF/OIF veterans referred to sleep and nightmare research: Are we studying a representative sample?* Poster presented at the annual meeting of the American Academy of Sleep Medicine, Baltimore, MD.

Paper presentation:

Cook, J., Harb, G. C. & Ross, R. (2013). *Imagery Rehearsal for posttraumatic nightmares: Observations from two clinical trials.* Presentation at the annual meeting of the European Society for Traumatic Stress Studies (ESTSS), Bologna, Italy.

Section V: Conclusions:

We have enrolled a total of 90 participants to date at the PA (84) and CT (6) sites. During the last 6 months, we were able to maintain a steady rate of recruitment. At this rate, we would complete enrollment of the target 115 in three additional quarters, that is, by March 2014. However, with existing funds and resources, we are able to continue to recruit until October 2013, placing enrollment at approximately 100. If we continue to enroll until October 2013, the last follow-ups will be completed in June or July of 2014. Thus, even if we stop recruitment in October 2013, we will require an extension to the project to complete data collection, cleaning and analysis, study closures and manuscript preparation.